Applicants' Remarks/Arguments

I. Status

Claims 1, 3-19, 21-28, 30-54 have been examined. Applicants have amended claims 3-10, 12-18, 21, 35-40 and 53-54. Accordingly, claims 1, 3-19, 21-28, 30-54 are presently pending and under Examination.

Claims 3-10, 12-18, 35, 37-39 and 53 have been amended to clarify that the recited aqueous gel is an aqueous gel separation medium. Support for this recitation may be found in the specification *inter alia* at page 11, lines 15-19 and at page 18, lines 26-28.

Claims 18, 36-39 and 54 have been amended to provide improved antecedent basis for the claims' recitation of "analytes." Support for the amendment may be found in the specification *inter alia* at page 7, lines 14-15; page 9, lines 3-4, page 15, lines 1-7, Figures 3-12 and original claim 1.

Claims 21 and 37-40 have been amended to recite that the one or more reagents claimed "help keep introduced analytes in a reduced form," in accordance with the suggestion of the Examiner. Support for the amendment can be found in the specification at page 7, line 23- page 8, line 2.

Claims 37-39 have been amended to improve antecedent basis, and to clarify that the hydrophilic polymers provide the structural framework of the claimed aqueous gel separation medium. Support for this recitation may be found at page 12, line 26-page 13, line 12.

Claim 39 has also been amended to specify that the capillary tube containing the aqueous gel separation medium has an uncoated inner surface. Support for this recitation may be found at page 7, lines 6-9, page 15, lines 23-27, and at page 18, line 23 – page 19, line 5.

No new matter has been introduced by any of the amendments.

II. The Interview Granted to Applicants on January 22, 2008

Applicants greatly appreciate the courtesy of the Examiner in granting a personal interview to the undersigned on January 22, 2008. At the interview, Applicants discussed the scope and content of U.S. Patent No. 5,370,777, and recitations that could be introduced into the claims to more clearly define the patentable subject matter of the present invention. Specifically, at the interview, Applicants discussed that the cited art failed to disclose a separation medium containing a tris borate buffer in the absence of a chaotropic agent, and that the cited **Guttman *et al.* '777** Patent does not relate to the uncoated tubes being presently claimed.

III. The Invention

The present invention relates to a novel aqueous electrophoresis gel medium and a capillary electrophoresis system comprising such a medium.

The ability to separate analytes has, in the past, been impacted by several problems. For example, only certain polymers are capable of separating polynucleotides and proteins (please see page 6, lines 21-23 of the Specification). Significantly, as analyte size increases, relative differences in charge diminish (please see page 2, lines 11-20; U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**) at column 2, lines 16-22). Accordingly, the art has recognized the desirability of employing detergents (such as sodium dodecyl sulfate) to denature large analytes (such as proteins and polypeptides) so that disparities in their effective charges will not distort the rate with which such molecules migrate through the electrophoretic matrix (please see **Guttman *et al.* '777** at column 2, lines 42 - 47). Such treatment, however, entails the use of a ***charged*** medium possessing a pH greater than 3. The use of such a medium causes the silanol groups of glass capillary tubes to ionize (please see page 6, lines 29-30 of the Specification). Aqueous gel media containing negatively charged detergents bind poorly to the capillary surface under such conditions (please see page 6, line 21 – page 7, line 2). Such poor binding causes undesirable electroendoosmotic flow and analyte-wall interactions that

distort the electrophoretic separation (please see, page 4, lines 14-15 of the Specification).

The art teaches that these problems may be addressed using capillary tubes having a ***permanently affixed*** coating on their internal surface (see, e.g., **Guttman *et al.*** '777 at column 6, lines 44-51, column 17, lines 8-18; please see Declaration of Dr. Liu at Paragraph 4C). But, this solution suffers from the problem that sample throughput is decreased and the coatings are often unstable under acidic or basic conditions. Moreover, crosslinking such coatings to the surface of the capillary tube can be time-consuming and expensive.

The present invention provides an alternative aqueous gel composition that may be used in initially uncoated capillary tubes because it forms a ***non-permanently affixed*** (*i.e.*, ***dynamic***) coating on the internal surface of capillary tubes and thereby renders them suitable for capillary electrophoresis (please see the Specification at page 18, lines 26-28; Declaration of Dr. Liu at Paragraph 4D).

IV. The Rejections Pursuant to 35 U.S.C. § 112, First Paragraph

Claims 3-10, 12-18, 21-28 and 30-54 are rejected pursuant to 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Specifically, the former Examiner has suggested that claims 37-39 should be amended to recite "reagents that function to ***help*** keep reagents in a reduced form." Applicants have amended the claims accordingly.

Additionally, the former Examiner has rejected claims 37-39 pursuant to 35 U.S.C. § 112, first paragraph, in light of the recitation "molecules of said hydrophilic polymers are entangled to provide said gel's structural framework and rigidity." Applicants' amendments to claims 37-39 have eliminated this recitation.

In light of Applicants' amendments and the above remarks, Applicants respectfully submit that the rejection of claims 3-10, 12-18, 21-28 and 30-54 pursuant to 35 U.S.C. § 112, first paragraph may now be properly withdrawn.

V. The Rejections Pursuant to 35 U.S.C. § 112, Second Paragraph

Claims 3-10, 12-18 and 37 are rejected pursuant to 35 U.S.C. § 112, second paragraph as being indefinite in light of the desirability for improved antecedent basis for the recitation "one or more reagent(s) that function to keep analytes in a reduced form." Applicants have amended claims 37-39, and respectfully submit that such amendment full responds to the former Examiner's concerns.

In light of Applicants' amendments and the above remarks, Applicants respectfully submit that the rejection of claims 3-10, 12-18 and 37 pursuant to 35 U.S.C. § 112, second paragraph may now be properly withdrawn.

VI. The Rejections Pursuant to 35 U.S.C. § 103(a)

A. The Rejection of Claims 3-9, 12-13, 16-18, 21-27, 30-31, 34-36, 48-49 and 52-54

Claims 3-9, 12-13, 16-18, 21-27, 30-31, 34-36, 48-49 and 52-54 have been rejected under 35 U.S.C. § 103(a) as unpatentable in light of U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**). **Guttman *et al.* '777** is stated to disclose an aqueous gel medium, comprising a non-cross-linked hydrophilic polymer, for facilitating the electrophoretic separation of analytes present in a sample. The former Examiner has suggested that **Guttman *et al.* '777** discloses an invention that is indistinguishable from that claimed by Applicants. Applicants respectfully traverse the rejection and request reconsideration.

1. The Aqueous Gel Separation Medium of the Present Invention Is Not Obvious in Light of Guttman *et al.* '777

Applicants have amended the claims of the application to more clearly describe the nature of the gel separation medium of the present invention, and respectfully submit

that the presently claimed invention is distinct from, and not obvious in light of **Guttman *et al.* '777**.

In summary, Applicants' aqueous gel separation medium ***consists essentially of*** a tris-borate buffer solution and a dissolved hydrophilic polymer. As the Examiner will recognize, **Guttman *et al.* '777** teaches the use of a tris-borate buffer solution ***only*** in concert with a chaotropic denaturation agent (i.e., 6-8 M urea or 3-8 M urea in the presence of 20-40% of a non-urea denaturing agent or 98% of a non-urea denaturing agent capable of disrupting hydrogen bonding; column 10, lines 21-54). There is no teaching, suggestion, motivation or prediction in the teachings of **Guttman *et al.* '777** to choose tris-borate buffer for use in any separation composition other than a denaturing one. In fact, as mentioned previously, the results obtained by using tris-borate buffer in the claimed invention were ***unexpected***. Applicants respectfully submit that in light of the ***express*** teaching of **Guttman *et al.* '777** to ***include*** a chaotropic denaturation agent in compositions having tris-borate buffers, the claimed gel separation medium that contains a tris-borate buffer, but ***lacks*** a chaotropic denaturation agent would not have been obvious.

The former Examiner has advised that the pH ranges recited in claim 37 would have been *prima facie* obvious in light of **Guttman *et al.* '777** (which is alleged to teach a pH range of 8.0-10.0, more expressly 8.0 – 8.5, and more specifically a pH of 8.3). Applicants respectfully submit that those of ordinary skill would not have drawn this conclusion. It is submitted that **Guttman *et al.* '777** does not teach, suggest, motivate or predict the pH of an aqueous gel separation medium containing a tris-borate buffer, but ***lacking*** a chaotropic denaturation agent.

The former Examiner has advised that **Guttman *et al.* '777** discloses the inclusion of reducing reagents such as dithiothreitol and 2-mercaptoethanol with the sample, and has suggested that such reducing reagents, by virtue of their small size, would diffuse into the gel material and thus serve to keep analytes in a reduced form. Applicants respectfully request reconsideration of this conclusion.

It is submitted that those of ordinary skill would have concluded that **Guttman *et al.* '777** teaches the use of a reducing reagent ***solely*** for the purpose of sample preparation; i.e., "***before introduction into the capillary column***" (see **Guttman *et al.* '777,** column 18, lines 41-42, emphasis added). It is therefore respectfully submitted that those of ordinary skill would not have drawn the conclusion reached by the former Examiner for at least two reasons:

1. The former Examiner's conclusion fails to address the fact that analyte molecules, by virtue of their size and charge will migrate in capillary electrophoresis and thus will separate ***away*** from the uncharged reducing reagents (please see page 2, lines 6-7 of the Specification). Accordingly, such reducing reagents, even if provided by **Guttman *et al.* '777**, would be ***incapable*** of functioning to help ***keep*** analytes in a reduced form, as is presently claimed, since the analytes and the reducing reagents *would be continuously migrating further and further apart*. As the Examiner will appreciate, even if charged reducing reagents were employed, such molecules would migrate faster than the larger protein analytes and would thus also separate from such analytes.
2. The formation of disulfide bonds is chemically favored unless the environment of the analyte is a reducing one, such as that created when a reducing agent is present. The former Examiner has proposed that **Guttman '777's** inclusion of reducing reagents such as dithiothreitol and 2-mercaptoethanol would create and maintain such a reducing environment. However, since any interaction between these reducing agents and the disulfide bonds upon which they would act would be a ***non***-covalent interaction, thermodynamic considerations would cause the reduced disulfide bonds to simply re-form as the analyte and reducing agent migrate away from each other. The –SH groups formed by interaction with a reducing agent would thus ***not*** serve to help ***keep*** the analyte in a reduced form.

In light of the active and/or differential mobility of the analytes, it is respectfully submitted that the method of **Guttman *et al.* '777** would provide no means for ***maintaining*** the concentration of such reducing reagents at a level sufficient to ***"help keep"*** analytes in a reduced form, as is presently claimed. Applicants therefore submit that those of ordinary skill would not have found it obvious in light of **Guttman *et al.* '777** to have included reducing reagent(s) that function to ***help keep*** protein analytes in a reduced form ***within*** the employed aqueous gel medium. Thus, the improvement provided by the present invention is more than the predictable use of prior art elements according to their established functions. Accordingly, Applicants submit that **Guttman *et al.* '777** does not render the presently claimed gel medium obvious.

2. The Electrophoretic Systems of the Present Invention Are Not Obvious in light of Guttman *et al.* '777

Claims 38 and 39, and their dependent claims, are submitted to be patentable over **Guttman *et al.* '777** at least in part because **Guttman *et al.* '777** provides no teaching, suggestion, motivation or prediction of a capillary electrophoresis system comprising a capillary tube containing the recited aqueous gel separation medium.

As the Examiner will note, **Guttman *et al.* '777** teaches "capillary columns comprising combinations of the following: (1) a bifunctional agent which is adsorbed to the inner wall of the capillary column; (2) a gel composition copolymerized with the bifunctional agent; (3) a hydrophilic polymer adsorbed onto the polyacrylamide gel; and (4) a separation composition substantially interspersed throughout the remainder of the column" (**Guttman *et al.* '777** at column 6, lines 44 – 51).

The former Examiner has advised that the Office interprets **Guttman *et al.* '777** as teaching the use of both permanently coated capillary tubes and uncoated capillary tubes. Applicants respectfully submit that **Guttman *et al.* '777** does not teach, suggest, motivate or predict, a capillary electrophoresis system comprising an aqueous gel separation medium with the ability to ***dynamically*** coat the inner surface of an uncoated capillary tube. Thus, the improvement provided by the present invention is more than the predictable use of prior art elements according to their established functions.

Accordingly, Applicants submit that **Guttman *et al.* '777** does not render the presently claimed capillary electrophoresis system obvious.

Applicants submit that **all** of **Guttman *et al.* '777's** proposed electrophoretic systems comprise ***at least*** a coating of a bifunctional crosslinking agent **covalently and permanently affixed** to the internal surface of the capillary tube. In this regard, Applicants respectfully draw the Examiner's attention to **Guttman *et al.* '777's** clear assertion of the ***permanence*** of the disclosed coating ***and its desirability***:

> "Because the bifunctional agent is presumptively adsorbed to the column via ionic forces; the polymer gel is crosslinked to the bifunctional agent; and the hydrophilic polymer is adsorbed to the polymer gel, these components are intended to be "permanently" affixed to the inner wall of the capillary column. The separation compositions, on the other hand, are not intended to be "permanently" affixed to the hydrophilic polymer. Accordingly, these compositions can be removed from the column such that the column can be regenerated. Thus, rather than having to replace the entire column after a series of analytical runs, an investigator can remove the separation composition from the column and regenerate that same column using another separation composition."

Guttman *et al.* '777, column 17, lines 8-22; see, also, Example III.

The present invention is predicated, in part, upon the recognition that by dissolving a hydrophilic polymer into a high concentration tris-borate buffer, a separation medium is produced which ***dynamically*** coats the internal surface of an uncoated capillary tube to *suppress* electroosmotic flow and *reduce* analyte-surface interactions. As a consequence, the claimed separation medium can be used in uncoated capillary tubes in capillary electrophoresis systems (please see the Specification at page 18, lines 26-28; Declaration of Dr. Liu at Paragraph 4D).

As discussed on page 12, line 26 – page 13, line 7 of the present Specification, Applicants' recognition of a gel separation medium capable of forming a dynamic coating was an ***unexpected*** result. In this regard, the Examiner's attention is respectfully directed to **Figure 2** (lower two curves) of the Application which shows the poor

resolution of capillary electrophoresis when conducted using hydrophilic polymers and uncoated capillary tubes. In contrast, the upper curve of **Figure 2** shows the capability of the aqueous medium of the present invention to act as a molecular sieve in capillary electrophoresis with uncoated capillary tubes.

Regarding claim 38 and its dependent claims, Applicants respectfully submit that, **Guttman *et al.*** '777 fails to teach, suggest, motivate or predict an aqueous gel separation medium that contains a tris-borate buffer, but ***lacks*** a chaotropic denaturation agent.

Likewise, additionally, **Guttman *et al.*** '777 does not teach, suggest, motivate or predict the pH of a gel electrophoresis medium containing a tris-borate buffer, but ***lacking*** a chaotropic denaturation agent or that is not cross-linked to the inner surface of the capillary tube.

Regarding claim 39 and its dependent claims, Applicants respectfully submit that **Guttman *et al.*** '777 fails to disclose a capillary gel electrophoresis system comprising a gel separation medium that **dynamically** coats the **uncoated** inner surface of a capillary tube.

Applicants respectfully submit that **Guttman *et al.*** '777 fails to teach, suggest, motivate or predict the claimed electrophoretic systems. In light of Applicants' amendments and the above remarks, Applicants respectfully submit that the rejection of claims 3-9, 12-13, 16-18, 21-27, 30-31, 34-36, 48-49 and 52-54 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,370,777 (**Guttman *et al.*** '777) may now be properly withdrawn.

B. The Rejection of Claims 10, 28 and 47

Claims 10, 28 and 47 have been rejected pursuant to 35 U.S.C. § 103(a) as obvious to one of ordinary skill in light of U.S. Patent No. 5,370,777 (**Guttman *et al.*** '777) in view of "Dextran Product Information", Sigma-Adrich (2001) found at http://www.sigmaaldrich.com/sigmaaldrich/product_information_sheet/d5376pis.pdf. The Dextran Product Information sheet is cited as evidence that commercially available

dextran possesses a non-cross-linked structure composed of approximately 95% alpha-D-(1-6) linkages. Applicants respectfully traverse and request reconsideration.

Applicants note that although the Dextran Product Information sheet discloses the nature and percentage of the dextran linkages, and indicates that Dextran of MW 2,000 kDa is commercially available, it does not appear to teach, suggest, motivate or predict the use of dextran compositions having the molecular weight recited in applicants' claims, nor does it remedy the above-discussed deficiencies of **Guttman *et al.* '777** with respect to the non-obviousness of the presently claimed invention. **Guttman *et al.* '777** does not remedy this deficiency, since it provides no basis for concluding either the inherency of dextran molecular weights or that the dextran employed by **Guttman *et al.* '777** meets the nature and percentage of the dextran linkages recited in the claims.

It is submitted that the combined teachings, suggestions, motivations, or predictions of the references thus fail to render the claimed invention obvious. Applicants respectfully submit that claims 10, 28 and 47 comprise the recitations of previously amended claims 1 and 19, and accordingly are patentable for the reasons stated with respect to such claims the rejections based on **Guttman *et al.* '777**. Thus, the improvement provided by the present invention is more than the predictable use of prior art elements according to their established functions. Accordingly, Applicants respectfully submit that the rejection of claims 10, 28 and 47 pursuant to 35 U.S.C. § 103(a) in light of U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**) as combined with "Dextran Product Information," Sigma-Adrich (2001) may now be properly withdrawn.

C. The Rejection of Claims 14-15, 32-33 and 50-51

Claims 14-15, 32-33 and 50-51 have been rejected pursuant to 35 U.S.C. § 103(a) as obvious to one of ordinary skill in light of U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**) in view of U.S. Patent No. 5,213,669 (**Guttman '669**). **Guttman '669** is stated to teach an aqueous gel medium having an alcohol that is glycerol. Applicants respectfully traverse and request reconsideration.

Applicants submit that claims 14-15, 32-33 and 50-51 comprise the recitations of claims 37-39, and accordingly are patentable over **Guttman *et al.* '777** for the reasons stated above. **Guttman '669** does not teach the use of tris-borate buffers. Accordingly, the hypothetical combination of **Guttman *et al.* '777 Guttman '669** would require selectively choosing to employ the alcohols taught by **Guttman '669** while eschewing the buffer systems that **Guttman '669** expressly teach to be required when using such alcohols; it would further require employing the tris-borate buffer taught by **Guttman *et al.* '777** while eschewing the chaotropic denaturation agent expressly taught by **Guttman *et al.* '777** as necessary when using such buffer. Applicants respectfully submit that such selective substitutions are not obvious and that the combination of **Guttman *et al.* '777** and **Guttman '669** fails to teach, suggest, motivate or predict the use of a tris borate buffer in the aqueous gel or capillary electrophoresis systems presently claimed. Additionally, Applicants note that the compositions recited within the presently claimed inventions provide unexpectedly better results than those obtainable using the compositions of **Guttman '669** (please see Example 5 of the present application). Thus, the improvement provided by the present invention is more than the predictable use of prior art elements according to their established functions. Accordingly, in light of Applicants' amendments and the above remarks, Applicants respectfully submit that the rejection of claims 14-15, 32-33 and 50-51 pursuant to 35 U.S.C. § 103(a) in light of U.S. Patent No. 5,370,777 (**Guttman *et al.* '777**) as combined with U.S. Patent No. 5,213,669 (**Guttman '669**) may now be properly withdrawn.

VII. Concluding Remarks

Applicants submit that the present response is complete and complies with the requirements of 35 U.S.C. §121. The Application is believed to be in condition for Allowance and early notice of such favorable action is respectfully requested. Should the Examiner have any questions regarding the subject invention or its patentability, Applicants encourage the Examiner to contact the undersigned to answer such questions or provide any desired additional information.

Respectfully Submitted,

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Edell, Shapiro & Finnan, LLC
1901 Research Boulevard, Suite 400
Rockville, MD 20850
Telephone: (301) 424-3640
Facsimile: (301) 762-4056

/Jeffrey I. Auerbach/
Jeffrey I. Auerbach
Registration No. 32,680
Attorney for Assignee

Customer No. **52287**